Radical Decarboxylative 1,2,3-Trifunctionalization of 3-Enoic Acids via 1,4-Imino-N Shift: A Modular Approach to Functionalized 3,4-Dihydroisoquinolines

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Key words: alkenyl carboxylic acids • radical reaction • rearrangement • trifunctionalization • decarboxylation •

Summary: A novel radical decarboxylative 1,2,3-trifunctionalization of various 3-enoic acids is achieved via 1,4-imino-N shift by using CF_3I as trifluoromethylating reagent and the readily available aryl ketoximes as both acid activator and difunctionalization reagent. This reaction is performed by CF_3-radical addition on the terminal alkene moiety of in-situ formed aryl ketoxime 3-enoates, followed by a cascade radical 1,4-imino-N shift/decarboxylation/arylation to furnish the N-atom at 2-position of alkenes and to fix the aryl group at 3-position by replacing the carboxyl group. Consequently, a series of 1,2,3-trifunctionalized allyl derivatives are efficient produced in the form of structurally important trifluoromethylated 3,4-dihydroisoquinolines (3,4-DHIQs). Other functional radicals such as diverse fluoroalkyl and azido radicals can also trigger the reaction. This tactic not only provides a new conversion mode for 3-enoic acids and aryl ketoximes, but also affords unprecedent modular method for constructing diverse functionalized 3,4-polysubstituted DHIQs with excellent regio- and diastereoselectivity and bioactive molecules compatibility.

INTRODUCTION

Free radical mediated alkene functionalization provides a simple, rapid and efficient tactic for the high value-added conversion of alkenes. Among them, the 1, 2-difunctionalization of olefins is well-established and comprehensive, and numerous cases have been reported up to now (Figure 1Aa).[1-4] Recently, the 1,3-difunctionalization of olefins is also revealed. For instance, Studer reported an elegant 1,3-difucntionalization of allylboronic ester with concomitant 1,2-boron shift by using alkynyl/azido triflones as the difunctionalization reagent (Figure 1Ab).[5] Bao subsequently realized a similar 1,3-fluroalkylalkynylation on α-vinyl-β-ketoesters by using the same difunctionalization reagent with the aid of the well-established 1,2-carbonyl migration Dowd–Beckwith ring expansion (Figure 1Ac).[6] In contrast, the site-selective long-distance radical continuous 1,2,n-trifunctionalization of alkenes, although with the advantages of richer site-selectivity and simultaneously introducing more functionalities, is rarely investigated due to the elusive method.[7] A promising approach to achieve this transformation is to employ the remote radical functional group rearrangement. [8,9] Very recently, we reported a unique dehydroxylative 1,2,4-/1,2,5-trifunctionalization of (bis)homoallylic alcohols by radical 1,4/5-methoxyphosphorous rearrangement mediated C- O bond dissociation to yield phosphorylated fluoroalkyl iodides (Figure 1Ad).[10] However, the existing examples are far from demand and the benefit of olefine long-range multi-functionalization strategies have not been fully appreciated, particularly in the conversion of simple chemicals and precise product-oriented synthesis.

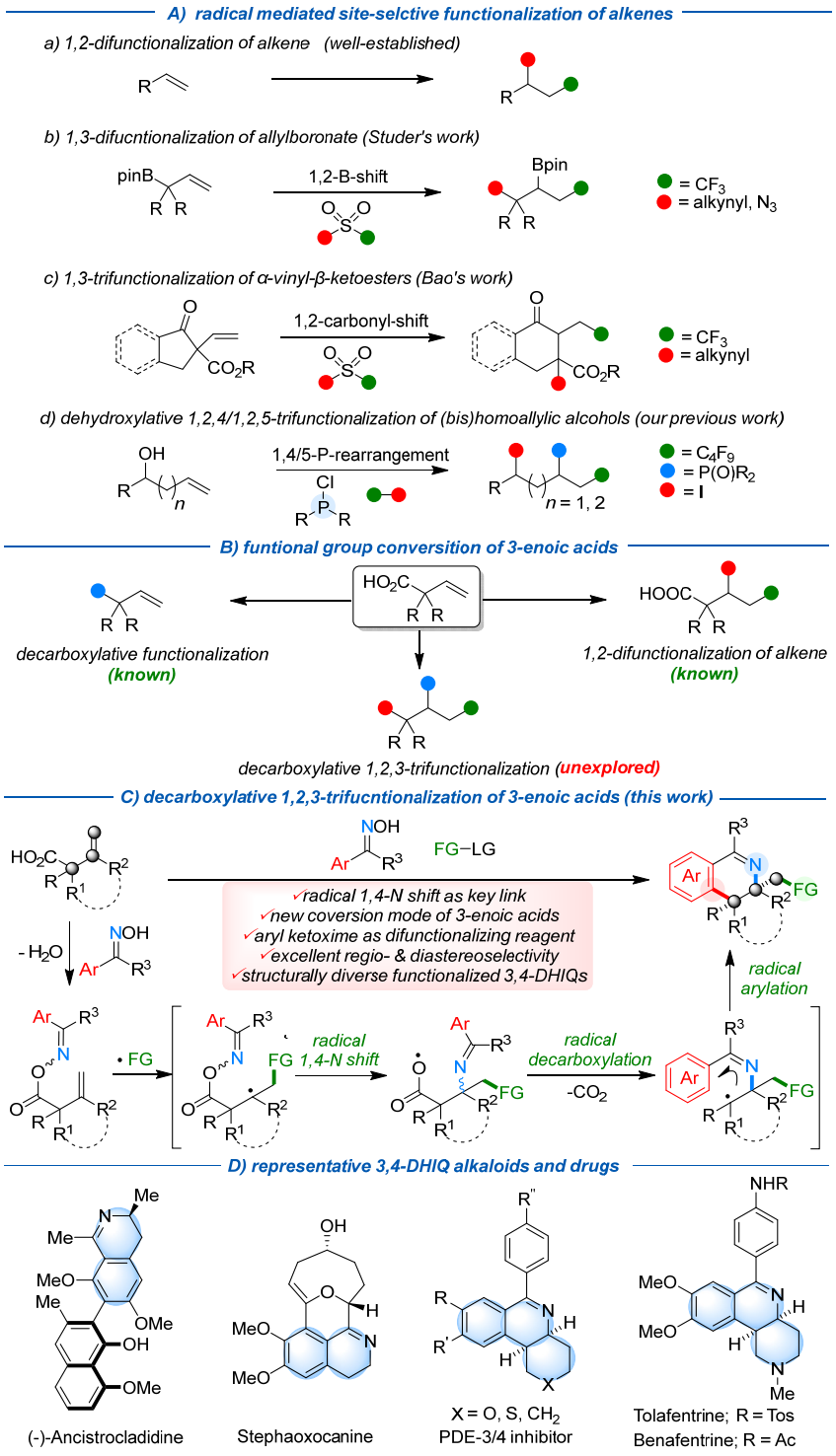


Figure 1. Di/trifunctionalization of alkenes and its synthetic applications

(A) Radical mediated site-selective functionalization of alkenes

(B) Functional conversion of 3-enoic acids

(C) Supposed radical decarboxylative 1,2,3-trifunctionalization of 3-enoic acids enabled by 1,4-imino-N shift.

(D) Representative 3,4-DHIQ alkaloids and drugs

Alkenyl carboxylic acids, especially 3-enoic acids, are readily accessible simple building blocks which play important roles in organic transformation.[11,12] Their functional group conversion mainly focuses on the decarboxylative

functionalization only as carboxylic acids[13] or the 1, 2-difunctionalization just as alkenes[14]. While the simultaneous combination of the decarboxylative functionalization and the alkene 1,2-difunctionalization leading to direct 1,2,3-trifunctionalization of 3-enoic acids in a reaction, to our best knowledge, has never been achieved (Figure 1B). Encouraged by our previous unique distal radical N-migration[15], we report herein an unprecedented radical decarboxylative 1,2,3-trifunctionalization of 3-enoic acids by a one-pot two-step reaction with aryl ketoximes and functional radical precursors. This approach is trigged by the addition of a functional radical to the terminal position of alkene moiety of the ketoxime esters formed in-situ from 3-enoic acids and aryl ketoximes, followed by a radical distal 1,4-N-migration/decarboxylation/arylation cascade (Figure 1C). Functional radicals such as structurally various fluoroalkyl radicals as well as azido radical are all effective in the reaction. Significantly, aryl ketoximes serve as both the activator of carboxylic group[16-18] and the radical difunctionalization reagent in this transformation, furnishing the N-atom at the 2-position of alkene and fixing the aryl group at allylic position (3-position) by the replacement of the carboxylic group. As products, a series of 1,2,3-trifunctionalized allyl derivatives are efficient produced in the form of structurally important functionalized 3,4-dihydroisoquinolines (3,4-DHIQs).

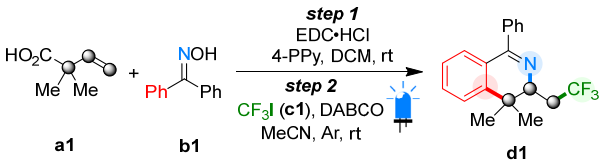
3,4-DHIQs, a subclass of isoquinolines,[19] constitute the core skeleton of a kind of alkaloid natural products[20,21] and bioactive molecules which possess prominent medicinal values (Figure 1D)[22,23]. Despite their efficient and diverse synthesis has attracted longstanding attention of chemists and pharmacologists, effective strategies to date are still limited[24-29]. Intramolecular electrophilic cyclization of the pre-synthesized acyl phenylethylamines (Bischler-Napieralski reaction[24]) and intermolecular [4+2] annulation of imines and alkenes/alkynyls are the dominant methods access to such compounds[25-28]. However, these strategies are neither to simultaneously introduce useful functionalities during skeleton construction nor to produce 3,4-persubstituted products bearing two adjacent all-carbon quaternary carbon stereocenters. Thus, the development of conceptually distinct alternatives is still needed in order to introduce a wider structural and functional diversity onto this theme. In this context, the present study not only reveals new reactivities of 3-enoic acids and aryl ketoximes, but also provides a novel modular strategy access to structurally diverse functionalized 3,4-polysubstituted DHIQs for the first time. Notably, this approach features excellent regio- and diastereoselectivity, scaffold diversity, and is compatible with many bioactive moieties such as amino acids, peptides, steroids and alkaloids.

RESULTS AND DISCUSSION

Our investigation commenced with a one-pot reaction of commercially available 2,2-dimethylbut-3-enoic acid **a1**, diphenylmethanone oxime **b1**, EDC•HCl, and 4-PPy, followed by the addition of functional group precursor and amines to initiate the radical reaction by an EDA (electron-donor acceptor) process. As the introduction of fluorine/fluoroalkyl into bioactive molecules can significantly enhance their metabolic stability, solubility, permeability and lipophilicity[30-34], CF_3 was chosen as the preferred attacking functional group in the reaction. A series of CF_3 radical precursors such as CF_3I, Togni's I/II and Umemoto's reagents were tested under the conditions of visible light irradiation and argon atmosphere at room temperature. To our delight, when CF_3I (**c1**) and DABCO were used as the EDA complex, the decarboxylative 1,2,3-trifunctionalation reaction took place smoothly and gave the desired trifunctionalized allyl derivative in the form of trifluoromethyl 3,4-DHIQ **d1** in 81% yield (Table 1, entry 1). Togni's I/II and Umemoto reagents were also effective in the reaction, but the yield of **d1** was unsatisfied (Table 1, entries 2-4). DABCO was crucial for the reaction, other amines such as Et_3N, DBU, TMEDA, and quinuclidine were inert for the reaction and no desired product **d1** was generated (Table 1, entries 5-8). The solvent test results in the step 2 reaction showed that acetonitrile was the

best one, while others such as methanol, THF, DMF, and EtOAc could not afford better results (Table 1, entries 9-13). In addition, blue light irradiation was essential for the reaction since no product **d1** was obtained without light irradiation, even if the reaction was heated to 60 °C (Table 1, entries 14 and 15). Langlois' reagent $NaSO_2CF_3$ was also effective in the reaction by employing $K_2S_2O_8$ as the extra oxidant under heating at 60 °C instead of light irradiation (Table 1, entry 16).

Table 1. Exploration of Reaction Conditions.[a,b]



Entry	Variation of Conditions of step 2	Yield (%)
1	None	81
2	Togni's I reagent instead of CF_3I	41
3	Togni's II reagent instead of CF_3I	22
4	Umemoto reagent instead of CF_3I	30
5	NEt_3 instead of DABCO	0
6	DBU instead of DABCO	0
7	quinuclidine instead of DABCO	0
8	TMEDA instead of DABCO	0
9	DCM instead of MeCN	62
10	DMF instead of MeCN	78
11	EtOAc instead of MeCN	38
12	THF instead of MeCN	46
13	MeOH instead of MeCN	0
14	without light irradiation	NR
15	heating at 60 °C instead light irradiation	NR
16[c]	$NaSO_2CF_3$ / $K_2S_2O_8$ instead of CF_3I/DABCO	56

[a]Reaction conditions: a mixture of **a1** (0.3 mmol, 1 equiv), **b1** (0.3 mmol, 1 equiv), EDC•HCl (3 equiv), and 4-PPy (1 equiv) in CH_2Cl_2 was stirred for 8 h. Then the solvent was removed under vacuum and a MeCN solution of CF_3I (**c1**, 2 equiv) and DABCO (1 equiv) was added. The mixture was stirred for additional 10 h under the irradiation of blue LEDs (light emitting diodes, 443 nm, 30 W). [b]Isolated yield. [c]A mixture of $NaSO_2CF_3$ (1.2 equiv) and $K_2S_2O_8$ (2 equiv) in acetone/H_2O (1:1, 3mL) was used as radical initiator in step 2 by heating at 60 °C. EDC = 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine, 4-PPy = 4-pyrrolidinopyridine, DABCO = 1,4-diazabicyclo[2.2.2]octane, TMEDA = N,N,N',N'-tetra- methylethylenediamine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DCM = dichloro-methane, THF = tetrahydrofuran, DMF =N,N-dimethylformamide.

With the optimal reaction conditions in hand (entry 1 in Table 1), we began to evaluate the suitability of this protocol by varying alkenyl carboxylic acids, aryl ketoximes, as well as other attack functional groups and the results are summarized in Figure 2-5. Firstly, the scope of alkenyl carboxylic acids was investigated as shown in Figure 2. The decarboxylative 1,2,3-trifunctionalization worked with both symmetrically and unsymmetrically linear 3-enoic acids. The former afforded racemic trifluoromethylated 3,4-DHIQs **d1** and **d2** in excellent yields, and the latter gave trifluoromethylated 3,4-DHIQs **d3-d5** in moderate yields with high diastereoselectivity. X-ray single-crystal diffraction

analysis confirmed that two methyl groups of 3,4-persubstituted **d4** are located on the same side of the azacyclic ring. This reaction was also suitable for cyclic 3-enoic acids. Symmetrical 3-enoic acid containing cyclopentyl, cyclohexyl and tetrahydropyranyl were successfully converted to CF_3-functionalized spirocyclic 3,4-DHIQs **d6-d8** in good yields. Unsymmetrical 5-7 membered carbocyclic 3-enoic acids with different side chains, such as methyl, butyl, 3-methoxypropyl, and cyanomethyl, were also good candidates in the trifunctionalization, providing 3,4-fused DHIQs **d9-d14** as sole cis-diastereoisomer in good yields. The cis-configuration was confirmed by X-ray single-crystal diffraction analysis of compound **d10**. Significantly, the practicality of this strategy was fully proved by a gram-scale synthesis of **d10** (1.48 g, 83% yield). Unsymmetrical heterocyclic 3-enoic acids bearing tetrahydrothiophene, tetrahydrothiopyran, tetrahydropyran, and piperidine were also compatible with the reaction, affording structurally diverse cis-fused products **d15-d18** as sole diastereomer in good yields.

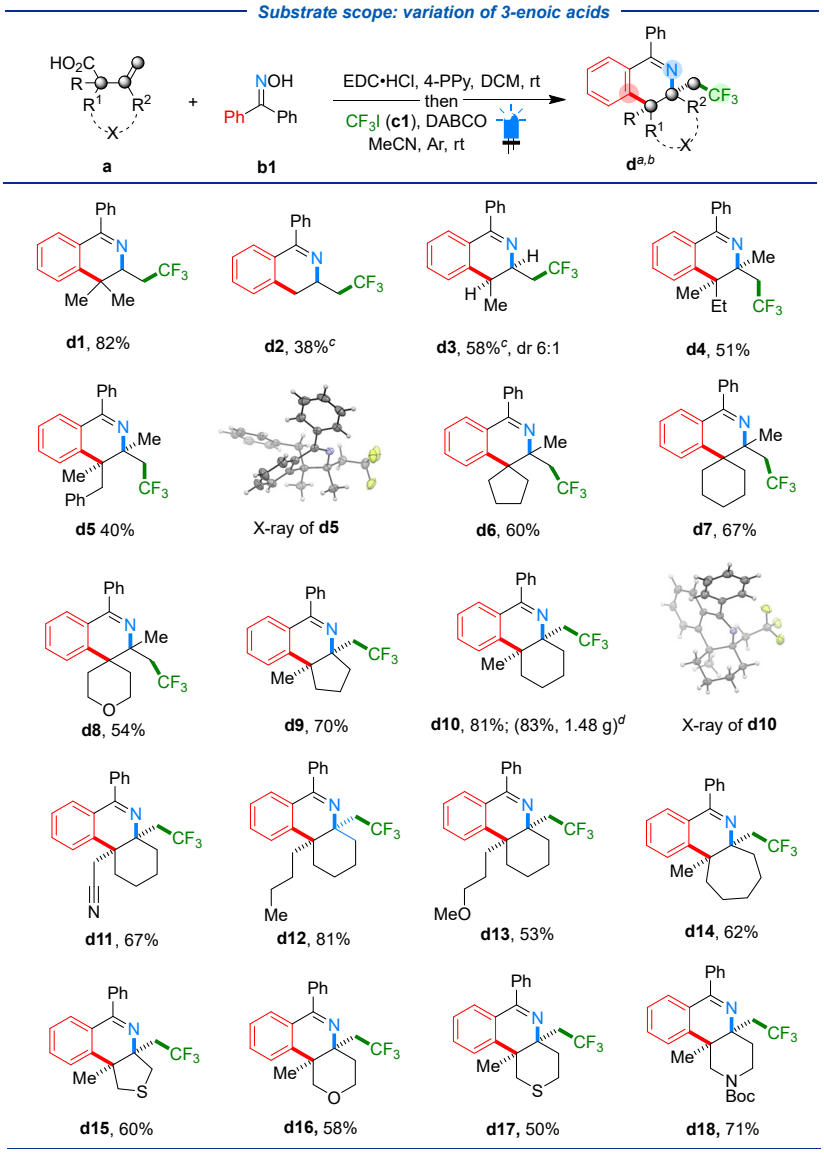


Figure 2. Variation of 3-enoic acids.[a,b] [a]Reaction conditions, see Entry 1 in Table 1. [b]Isolated yields. Unless otherwise noted, a single diastereomer was observed by ^{1}H NMR. [c]Reaction conditions, see Entry 16 in Table 1. [d]Gram-scale reaction was carried out on 5 mmol.

Next, the scope of ketoximes was explored by using cyclohexyl merged unsymmetrical 3-enoic acid **d10** as the reaction partner (Figure 3). Symmetrical diphenyl ketoximes bearing substituents with different electronic properties at

the para-position of phenyl ring such as NHAc, MeO, Me, F, Cl, Br, CN, and CO_2Me participated very well in the reaction, providing the corresponding trifluoromethylated 3,4-DHIQs **d19-d26** in good to excellent yields with sole cis-diastereoselectivity. Both ortho-Cl and meta-CF3 substituted symmetrical diphenyl ketoximes were good partners for the conversion, the former produced the corresponding 3,4-DHIQ **d27** in 56% yield, and the latter gave the product **d28** in 31% yield with only para-regioselectivity probably due to the steric of the substituent. 2,4-Dimethyl substituted benzophenone oxime was also a good candidate, as demonstrated in the case of **d29**. When asymmetric 4-(4-methoxybenzoyl)phenone ketoxime was involved the reaction, a mixture of cis-3,4-DHIQs **d30** and **d30'** was obtained in 68% yield with 1:1 ratio of chemoselectivity. Asymmetric diaryl ketoximes such as naphthalen-2-yl(phenyl)methanone, phenyl(thiophen-2-yl)methanone, phenyl (furan-2-yl)methanone, and phenyl(pyridin-2-yl)methanone oximes took place selective arylation on the phenyl ring rather than heteroarene to produce the corresponding cis-3,4-DHIQs **d31-d34** in moderate yields. Besides diaryl ketoxime, monophenyl ketoximes such as trifluoroacetophenone, N-butyl/N-cyclohexyl 2-oxo-2-phenylacetamides, and 2-(pyrrolidin-1-yl)-2-oxoacetyl benzene oximes also showed good compatibility with this protocol, delivering **d35-d38** in moderate yields.

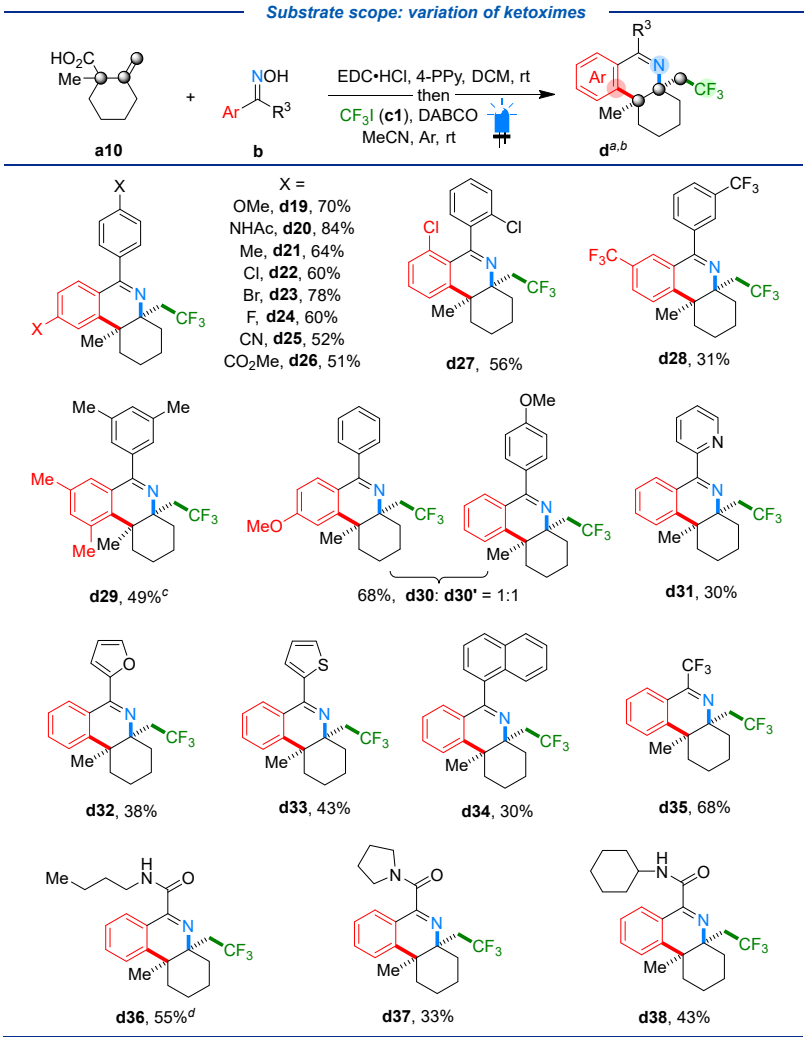


Figure 3. Ketoximes scope[a,b]: [a]Reaction conditions, see Entry 1 in Table 1. [b]Isolated yields. Unless otherwise noted, a single diastereomer was observed by ^1H NMR. [c]The usage amount of CF_3I was 1 equiv. [d]Ketoxime 3-enoate was used as substrate.

To further demonstrate the applicability of this method, structurally complicated 3-enoic acids and aryl ketoximes

containing bioactive molecules were investigated as well (Figure 4). As demonstrated in the case **d39**, nortropane merged 3-enoic acids smoothly underwent the decarboxylative 1,2,3-trifunctionalitzation to yield bridged polycyclic cis-3,4-DHIQs in 40 % yield with 1:1 ratio of exo:endo. In addition, amino acid ester, peptide, alkaloid, and steroid were also tolerant to the transformation when incorporated in aryl ketoximes, as in the cases **d40-d44** with complex structure.

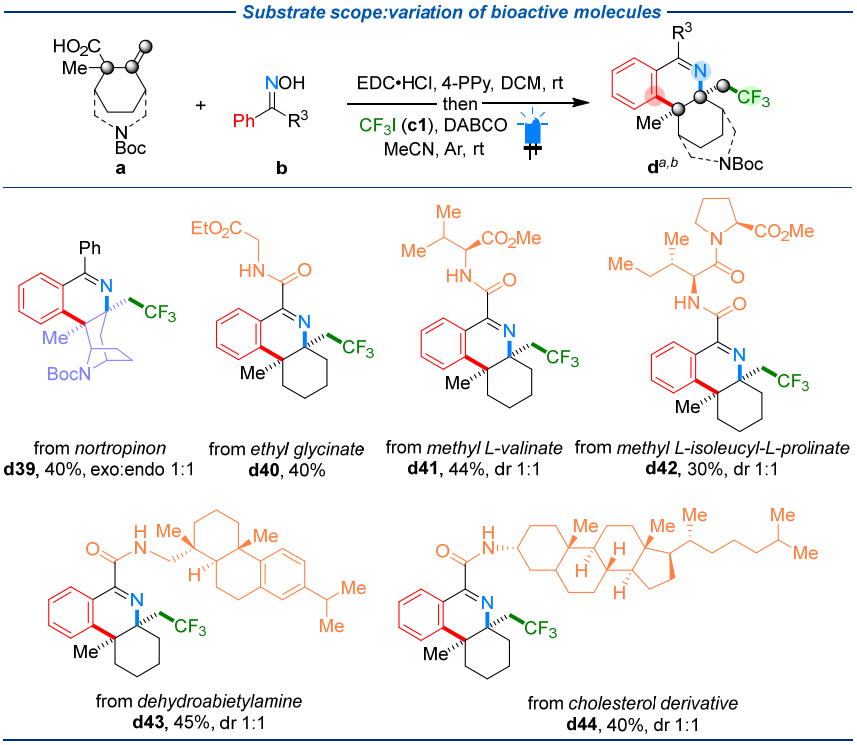


Figure 4. Compatibility of bioactive molecules[a,b]: [a]Reaction conditions, see Entry 1 in Table 1. [b]Isolated yields. Unless otherwise noted, a single diastereomer was observed by ^{1}H NMR.

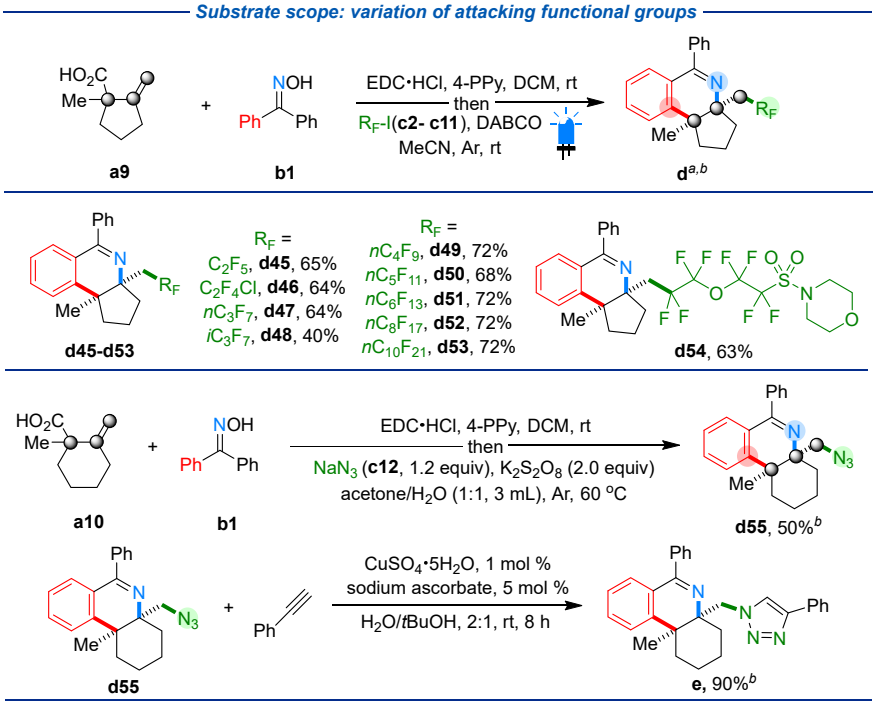


Figure 5. Scope of attacking functionalities[a,b]: [a]Reaction conditions, see Entry 1 in Table 1. [b]Isolated yields. Unless otherwise noted, a single diastereomer was observed by ^{1}H NMR.

Besides trifluoromethylation, other fluoroalkylations were well participated in the reaction by utilizing a wide array of linear, branched, and heteroatom embedded fluoroalkyl iodides as the luoroalkylating reagents, producing the corresponding fluoroalkyl-featured 3,4-DHIQs **d45-d54** in excellent yields (Figure 5). It is worth noting that azido radical could also effectively initiate this trifunctionalization to deliver the azido-featured 3,4-DHIQs **d55** in good yield. When compound **d55** was further treated with phenylacetylene under copper catalyzed click reaction conditions, the triazole-incorporated 3,4-DHIQs **e** was generated in 90% yield (Figure 5).

To account for the reaction mechanism, some control experiments were carried out as depicted in Figure 6. The esterification of 3-enioc acid **a10** with diphenyl ketoxime **b1** under the conditions of EDC•HCl and 4-PPy almost quantitatively gave the ketoxime carboxylate **I-1**. When **I-1** was subjected to the photoreaction conditions with CF_3I and DABCO, the reaction took place smoothly and gave **d1** in 88% yield. The formation and subsequent transformation of the crucial intermediate ketoxime ester disclose that aryl ketoxime does paly the dual roles of acid activator and difunctionalization reagent. The quantum yield of this reaction was determined to be $\Phi = 35$, indicating that a radical chain process is extremely operative (See Supporting Information for details). In addition, the measured intramolecular competitive kinetic isotope experiment (KIE) value was 1.27, revealing that the rate-determination step is not the C-H bond dissociation process.

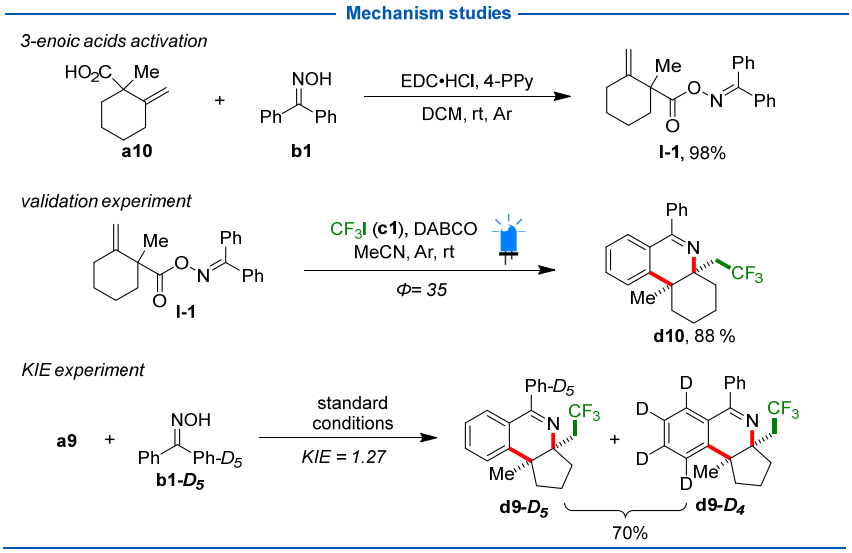


Figure 6. Mechanism studies.

On the basis of our experiments and literature report,[15,35] a proposed reaction mechanism is illustrated in Figure 7A by a representative sample. The activation of **a10** by **b1** under the dehydration conditions of EDC•HCl and 4-PPy first produces the ketoxime 3-enoate **I-1**.[36] Then CF_3 radical, which generates from the irradiation of the EDA complex of CF_3I and DABCO by blue light,[37] adds onto the alkene moiety of **I-1** through the transition state **TS1** (10.9 kcal/mol) to yield the carbon-centered radical intermediate **II** (see Supporting Information for the details of density functional theory (DFT) calculations). **II** undergoes a fast 5-exo-trig radical cyclization onto the N-atom of N=C bond to yield the carbon radical intermediate **III** across an energy barrier of 9.7 kcal/mol (**TS2**), the latter immediately experiences radical β-fragmentation with a low energy barrier of 3.6 kcal/mol (**TS3**) to form the carboxyl radical intermediate **IV**. The calculated Gibbs free energy change of this radical N-centered imino rearrangement is -7.9 kcal/mol. This is an obvious exothermic process, as it involves the cleavage of weak N-O bond of oxime ester with low bond dissociation energy

(BDE, ~57 kcal/mol) and the forming relatively strong C-N bond with higher BDE (~68 kcal/mol).[38] **IV** subsequently undergoes a kinetically and thermodynamically favorable radical decarboxylation process through **TS4** (6.3 kcal/mol) to release CO_2 to form the carbon radical **V**.[39,40] **V** is then trapped by the tethered phenyl ring via a cis-arylation to generate the intermediate **VI** through **TS5**, using an activation energy of 9.9 kcal/mol. Then a single-electron transfer (SET) process takes place between **VI** and CF_3I to produce the carbocation **VII**, CF_3 radical, and iodide, realizing the radical chain propagation.[41,42] Finally, **VII** is deprotonated by DABCO to accomplish the intramolecular aromatic homolysis substitution, yielding the trifluoromethylated 3,4-DHIQ **d10**.

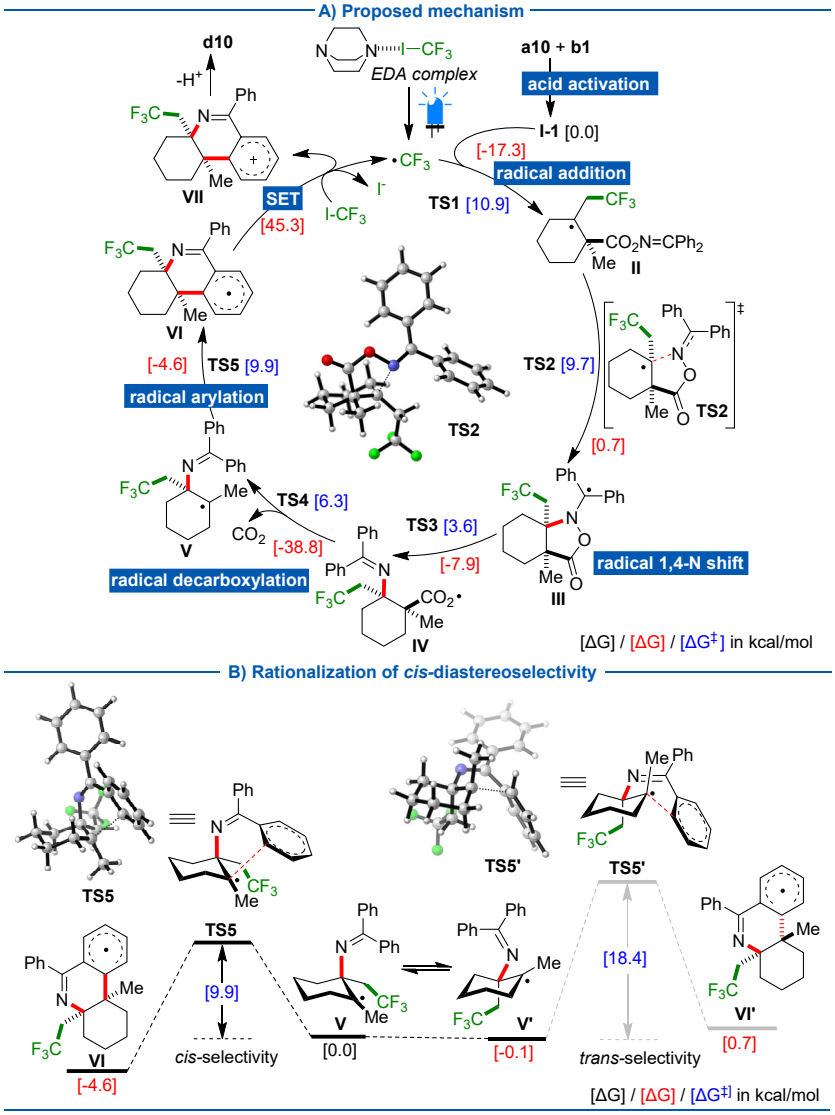


Figure 7. Proposed mechanism and DFT calculation.

A Proposed mechanism.

B Rationalization of cis-diastereoselectivity

To explain the observed sole cis-diastereoselectivity of **d10**, we calculated and compared the two processes of cis-/trans-intramolecular arylation that determine the diastereoselectivity of the product, as shown in Figure 7B. As aforementioned, the calculated activation energy of the transition state **TS5** through the cis-cyclization of the radical intermediate **V** is 9.9 kcal/mol. By contrast, when **V** flipped to the conformer **V'**, the latter can undergo the trans-cyclization through transition state **TS5'**, and the calculated energy barrier is 18.4 kcal/mol. Such a significant energy

barrier difference (8.5 kcal/mol) between two transition states **TS5** and **TS5'** determines the absolute dominance of cis-diastereoselectivity of the reaction since the Gibbs free energies of two conformers **V** and **V'** are almost equal.

CONLIUSION

In summary, we have successfully developed an unprecedented decarboxylative 1,2,3-trifunctionalization of various 3-enoic acids accompanied by 1,4-imino N-shift. This reaction is triggered by functional radicals such as fluoroalkyl and azido radicals and employs aryl ketoximes as both acid activator and difunctionalization reagent. As products, 1,2,3-trifuctionalizaed allyls are efficient produced in the form of structurally important functionalized 3,4-DHIQs with excellent regio- and diastereoselectivity. The protocol not only reveals unknown reaction mode of readily accessible 3-enoic acids and aryl ketoximes by employing unusual 1,4-imino-N shift, but also develop a conceptually new strategy for the synthesis of diverse functionalized 3,4-DHIQs through simultaneous skeleton construction and functional group introduction. Mechanism studies also confirms this reaction involves a radical sequence of addition/1,4-imino-N shift/ decarboxylative arylation. The stereochemical course of 1,4-imino-N shift and the excellent diastereoselectivity of subsequent C-radical arylation is also rationalized by DFT calculations.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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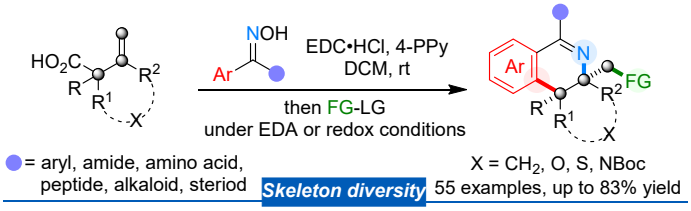
TOC



3,4-Dihydroisoquinolines are the core skeleton of a kind of alkaloids and many bioactive molecules. Despite their apparent utility, the simultaneous introduction of functionalities during skeleton construction is unreachable via established method. We present herein a conceptually new one-pot protocol access to functionalized 3,4-dihydroisoquinolines by an unprecedent 1,4-imino-N-shift promoted radical decarboxylative 1,2,3-trifunctionalization of readily accessible 3-enoic acids using aryl ketoximes and functional radical precursors. Aryl ketoximes serve as both the activator of carboxylic group and the radical difunctionalization reagent in the reaction. The study not only reveals new reactivities of 3-enoic acids and aryl ketoximes, but also provides a novel modular strategy access to structurally diverse functionalized 3,4-polysubstituted DHIQs for the first time which has positive implication for its pharmacal development.